SnapShot: Local Protein Translation in Dendrites

Neuron

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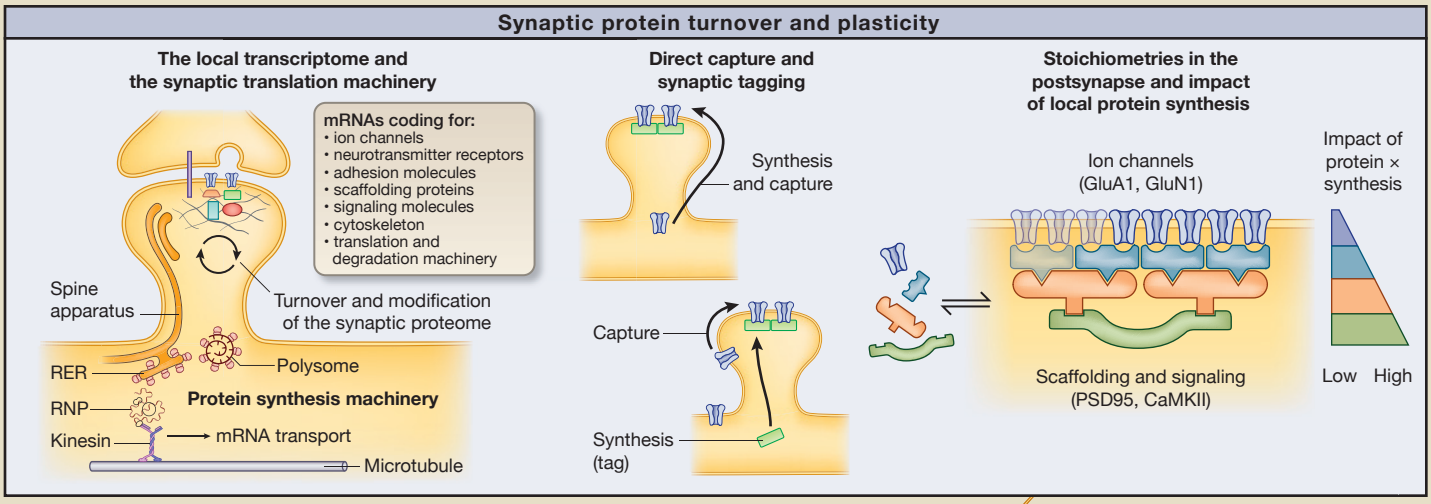
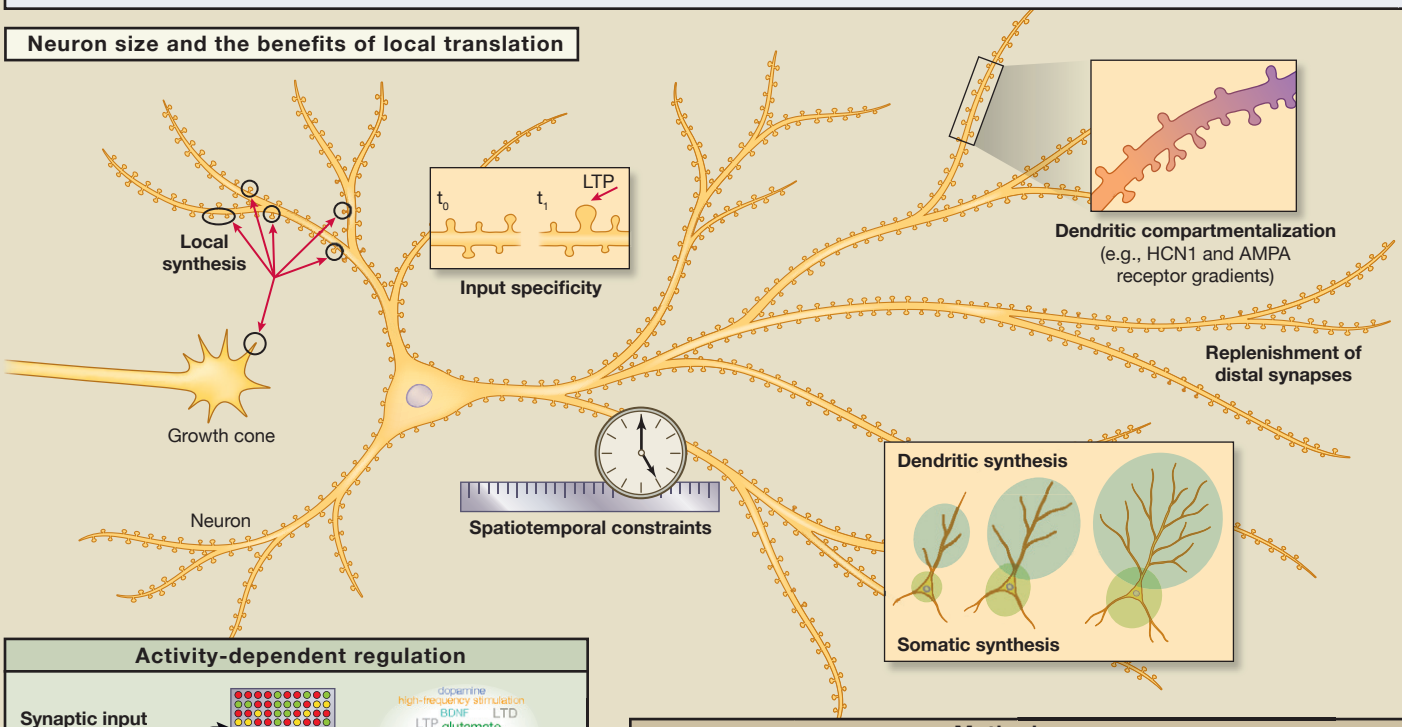
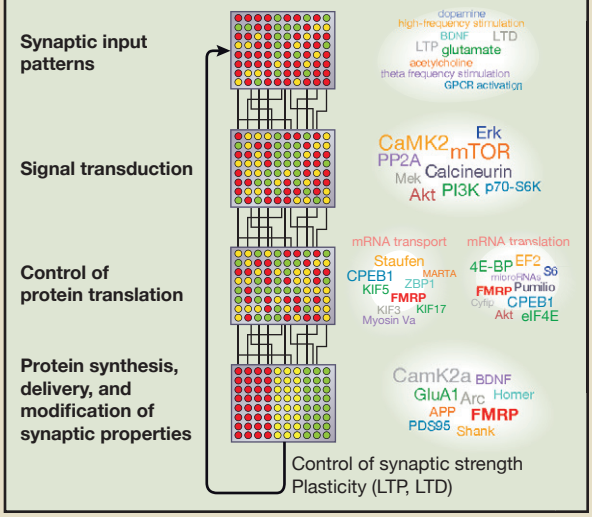
Synaptic protein turnover and plasticity



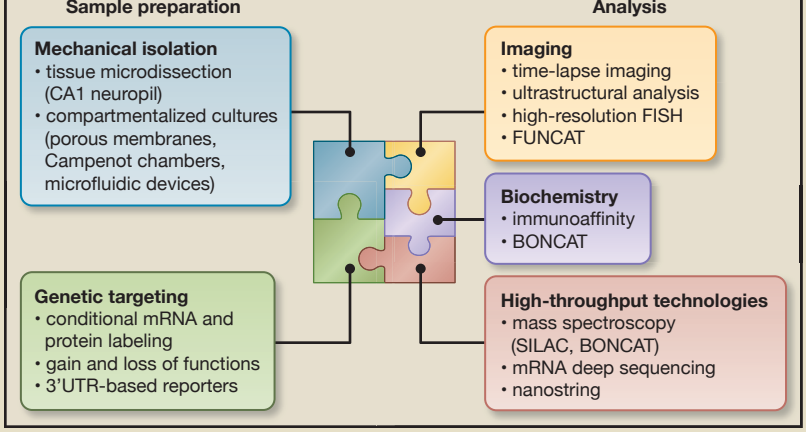
Neuron size and the benefits of local translation



Activity-dependent regulation



Methods



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mRNA localization and regulated translation provide an efficient means to spatially and temporally control gene expression in polarized cells. This is all the more important in neurons where local and timely changes of the proteome in growth cones and synapses, located up to hundreds of microns from the cell body, are required during brain development and plasticity.

The identity and distribution of dendritic mRNAs, transport mechanisms, and translational regulation during synaptic plasticity in normal and diseased neurons have been a major focus of investigation. It is now clear that local protein synthesis is a major regulator of input-specific and long-lasting changes in synaptic transmission. Yet, its more general role in neuron proteostasis is still poorly understood.

Here we highlight a number of key aspects of local protein translation in dendrites, with an emphasis on synaptic turnover and plasticity, neuronal size and morphological complexity, activity-dependent regulation, and the ideal toolbox that is needed to study these processes.

Protein Turnover and Synaptic Plasticity

Dendrites contain virtually all the cellular machinery required to synthesize proteins. Together with the intrinsic turnover of synaptic proteins, the control of mRNA transport, localization, and translation is a key determinant of local synaptic composition and function.

Initially thought to contain only a handful of transcripts, dendrites and axons are now known to include thousands of mRNA species representing most protein families, suggesting that local translation is the rule rather than the exception.

Due to the layered organization of the synapse, local translation may change synaptic composition, for example, by changing the population of receptors (direct synthesis and stabilization) or receptor binding proteins, allowing the recruitment of receptors taken from a more diffuse pool (synaptic tagging and capture).

The copy numbers of proteins at an individual synapse vary from tens of molecules up to hundreds, with binding stoichiometries that differ greatly between distinct classes of synaptic proteins. This implies that, all things being equal (e.g., protein stability and local turnover), the local production and recruitment of proteins with more binding slots and binding partners can have a magnified impact on synaptic composition. The local translation of just a few master proteins may thus have a more profound impact on synaptic properties than adding receptors “one by one.”

Neuron Size and the Benefits of Local Translation

Although the definition of the minimal functional unit of synaptic integration—the individual synapse, a dendritic branchlet—is still debated, it is clear that the composition and properties of this unit can be adjusted in an input- or dendrite-specific manner. Together with the size and morphological complexity of neurons, this functional compartmentalization sets unique spatiotemporal constraints on cellular metabolism.

Above a certain axonal and dendritic arbor size and complexity, the soma may not be sufficient to provide enough proteins for the entire cell. This may be due to “natural” limits of the biosynthetic capacity of the soma, which may need additional synthesis sites. As protein lifetime may be on the order of several days, protein synthesized locally may accumulate over time throughout the entire neuron. In addition, local sites of protein synthesis may be required to ensure that essential proteins with shorter lifetimes are available within adequate time frames, to avoid degradation or capture en route from the soma to distal targets.

It is expected that the potential impact of local protein synthesis will be determined by local mRNA levels and their actual translation and, once proteins are made, their lifespan and local retention. Yet, it is still not clear how these parameters are adjusted to change protein composition on different spatial scales (e.g., a single synapse or dendritic segment).

Activity-Dependent Regulation

Although signaling cascades regulating local translation are emerging, a more global understanding of proteostasis in neurons is lacking. It is now clear that synaptic activity regulates protein translation at multiple levels (mRNA transport and stability, generic and mRNA-group specific regulation), through intermingled signaling pathways. Although candidate approaches may be useful to implicate a specific signaling molecule in an experimentally defined context, it is unlikely that any behaviorally relevant activity-dependent translational program will be adequately described by adjustments of a few molecules or simple linear signaling cascades. At the two extremes, minor (and most likely overlooked) changes in the recent activity history of a neuron may set a different context and hence a completely different outcome for apparently similar stimulation paradigms, whereas synaptic plasticity induction protocols thought to be clearly distinct may converge on the same signaling pathways. This question is particularly important in genetic diseases where mutations in proteins involved in multiple aspects of mRNA trafficking and translation (e.g., FRMP) may perturb the homeostatic baseline of the synapse.

Experimental Procedures

Owing to the complexity of underlying signaling cascades, the multiple orders of magnitude of spatial scales to be considered (e.g., the individual synapse versus the entire dendritic tree) and the multiple neuron types that are involved, the ideal toolbox to study dendritic translation should include both high-resolution (e.g., single-protein tracking, in situ hybridization, etc.) and high-throughput (e.g., deep sequencing, mass spectrometry, etc.) methods, as well as genetic (e.g., genome engineering) and anatomical (e.g., brain slices, microdissections) means to reduce sample complexity by focusing selectively on specific cell types and subcellular compartments.

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